Remarks/Arguments

Prior to the present amendments, claims 1-3, 8 and 11 were pending in this application and were rejected on various grounds. Claims 3 and 11 have been canceled, claims 1 and 8 have been amended. Accordingly, claims 1, 2 and 8 are now pending. The amendments to the claims are fully supported by the specification as originally filed, and do not introduce new matter. In particular, the amendment of claim 8 is of formal nature. The amendment of claim 1 is supported at least by the working example and original Figure 1. All amendments are made without any disclaimer or prejudice. Applicant specifically reserves the right to pursue any deleted subject matter in one or more continuing applications.

Claim Objections

(1) According to the Examiner, claims 1-3, 8, and 11, as amended in Applicant's response to the previous Office Action, include an invention independent and distinct from the invention originally claimed. In particular, the Examiner notes that the amended claims, to the extent they recite an *in vitro* method for inhibiting the production of mdm2, include subject matter that is independent and distinct from the elected invention, *i.e.*, an *in vitro* method comprising disrupting the binding of human p53 and mdm2. As a result, claims 1-3, 8, and 11 have been objected to because part of these claims was drawn to a non-elected invention. The current claim amendments are believed to obviate this objection.

(2) Claims 1-3, 8, and 11 were additionally objected to for their use of the language "mdm2" as the sole means of identifying the protein for use in the claimed method, "because different laboratories may use the same laboratory designations to define completely distinct protein." Applicant was requested to include in the claims "physical and/or functional characteristics of mdm2, which unambiguously define mdm2."

This objection is respectfully traversed. Contrary to the Examiner's assertion, "mdm2" is not a "laboratory designation" rather a well known and generally used name for a known protein, not unlike the designation "p53," which is known and generally understood to designate a particular tumor suppressor protein. As stated on page 1, lines 35-36 of the specification, the cDNA sequence of human mdm2 is set out in WO 93/20238, a PCT application published as

early as 1993. The fact that "mdm2" is a uniformly used and accepted designation is further supported by the scientific art, including the references cited on pages 36 to 38 of the present application, and the papers cited by the Examiner in support of some of the rejections raised in the present Office Action. Thus, for example, McCann *et al., British Journal of Cancer* (1995) 72, 981-985, authored by scientists from the University College Dublin, uses this designation, noting that the human mdm2 gene was cloned and localized to chromosome 12q13-14 in 1992 (page 891, first column). The same designation is used in Quesnel *et al., British Journal of Hematology*, 1994, 88, 415-418, co-authored by scientists from two different French research facilities and the Bournemouth Hospital, UK. McCann *et al.* and Quesnel *et al.* cite the same 1992 Oliner *et al. Nature* paper in their reference to the human mdm2 sequence, therefore, there can be absolutely no doubt that they refer to the same protein. Since "mdm2" is well known and has been consistently referred to and known by this name by those skilled in the art for more than a decade, the Examiner is respectfully requested to reconsider and withdraw the present objection.

Rejection under 35 U.S.C. 112, first paragraph – Written description

Claims 1-3, 8, and 11 were rejected under 35 U.S.C. 112, first paragraph for allegedly lacking an adequate written description support in the specification. According to the rejection, based on the teaching in the art, one cannot predict that polypeptides having the motif FxaaXaaXaaW (SEQ ID NO: 4), other than those comprising SEQ ID NO: 3, would have the function (ability to disrupt the binding of p53 and mdm2) required by the claims. Bottger *et al.*, Oncogene, 1996, 13:2141-2147 was cited in support of this assertion. The Examiner further notes that the claims encompass polypeptides less than 25 amino acids in length, including polypeptides having less than 10 amino acids, such as hexapeptides, and cited Bottger *et al.* for the alleged teaching that no mdm2 binding phage could be isolated from a hexapeptide library, and that hexapeptides cannot provide sufficient correctly spaced contact points to bind the mdm2 binding pocket with high enough affinity. From this, the Examiner concludes that "the single disclosed peptide of SEQ ID NO: 3, that could adequately disrupt and displace p53 from binding mdm2, resulting in sufficient increase in the level of p53, similar to that induced by UV, is not a representative species of the claimed genus of polypeptides for use in the claimed method." (Page 9, first paragraph of the Office Action.)

Claims 3 and 11 have been canceled, therefore their rejection is moot. The rejection of the remaining claims is respectfully traversed.

Without acquiescing to the Examiner's position, or the reasoning underlying the Examiner's position, the claims now recite the use of peptides, less than 25 amino acids in length, that comprise SEQ ID NO: 3. Since, as the Examiner has acknowledged, the peptide of SEQ ID NO: 3 has been demonstrated to have the function necessary for use in the claimed method, it is a representative species of the claimed genus, which requires its presence. Accordingly, the specification provides adequate written description for the invention claimed, and the present rejection should be withdrawn.

Rejection under 35 U.S.C. 112, first paragraph – Enablement

Claims 1-3, 8, and 11 were rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. According to the rejection, "[e]xcept for the peptide consisting of SEQ ID NO: 3, one cannot predict whether the claimed peptides would have adequate inhibitor activity to displace an adequate number of p53 from binding to mdm2, resulting in a sufficient increase in the induction of p53 activity, similar to p53 induction by UV, such that cell cycle arrest or apoptosis could be induced." The Examiner adds that, even the rejection on these grounds could be overcome, claims 3 and 11 would still remain rejected for alleged lack of enablement, due to their recitation of "a portion of human p53."

Claims 3 and 11 have been canceled, therefore, their rejection is moot. Applicant respectfully traverses the rejection as it applies to the remaining claims.

The claims, as currently amended, recite the use of polypeptides, less than 25 amino acids in length, that comprise SEQ ID NO: 3. The requirement that the peptides should include the entire sequences of SEQ ID NO: 3 (which has been acknowledged to be enabled), coupled with the length limitation, defines a rather narrow genus, which is clearly enabled by the specification. There is nothing of record that would suggest that the addition of no more than six amino acids to the core sequence of SEQ ID NO: 3 would be expected to destroy its ability to function as it is required by the claim language. As the Examiner is well aware, even if some experimentation might be necessary to confirm that a claimed peptide within the scope of the claims has the

required function, such experimentation is not necessarily undue. A considerable amount of experimentation is permissible, if it is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Since the present specification provides detailed guidance for testing the ability of a candidate peptide for use in the claimed methods to disrupt the binding of p53 and mdm2, the invention can be practiced within the full scope of the claims currently pending without undue experimentation, and thus the claims are enabled. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejection under 35 USC 103

Claims 1-2 and 8 were rejected under 35 U.S.C. 103(a) "as being unpatentbale over Bottger *et al.*, 1996, *Oncogene*, 13:214-2147, of record, in view of McCann AH *et al.*, 1995, *British J. Cancer*, 71(5):981-5, or Quesnel B *et al.*, 1994, *Brit J. Haematology*, 88:415-418, and further in view of Lee JM *et al.*, 1995, *Cancer and metastasis* Review, 14(2):149-161.

Bottger *et al.* was cited for teaching that the oncogene mdm2 and its human homologue hdm2 bind to the tumor suppressor protein p53 and inactivates its function as a positive transcriptional factor, and that the mdm2-p53 interaction is a much pursued target for the development of anti-cancer drugs. Bottger *et al.* was further relied on (1) for its disclosure of a peptide, clone 12/1, having the consensus PXFXDYWXXL, which "could significantly inhibit the binding of p53 and mdm3;" (2) for allegedly teaching that "the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors;" and (3) for its alleged teaching that "the peptide was selected for improved stability and for its better conformational fit into the hdm2 binding pocket of p53. The Examiner has acknowledged that Bottger *et al.* "do not teach an *in vitro* method for disrupting the binding of p53 and mdm2 in a population of cancer cells in which mdm2 is not overexpressed."

McCann *et al.* was relied on for teaching expression of mdm2 in breast carcinoma and its association with low level of p53, and for allegedly teaching that "mdm2 amplification only occurs at a low frequency in breast cancer, as compared to non-epithelial tumors, and that in one of the amplified samples, there is no apparent alteration in mdm2 protein expression."

Quesnel B *et al.* was cited for teaching that "in myelodysplastic syndrome, there is no amplificaion, nore over-expression of mdm2 gene," and that "in heamatological malignancies, such as leukemia and lymphoma, there is no amplification of mdm2, and an over-expression of mdm2 is found only in a small proportion of the cases."

Lee JM was relied on for allegedly teaching that "p53 could induce apoptosis and cell cycle arrest, and that loss of p53 function causes increased resistance to chemotherapeutic agents." Lee JM was further cited for its alleged teaching that p53 functions as a transcriptional factor, view binding to specific DNA.

According to the rejection, it "would have been *prima facie* obvious to use the peptide taught by Bottger *et al.* to disrupt the binding of p53 and mdm2 in tumor cells, to increase the activity of p53, as taught by Bottger *et al.*," and it "would have been obvious to target any cancer cells that express p53 and mdm2, including those populations of cancer cells that do not overexpress mdm2, such as in breast cancer cells, taught by McCann *et al.* or hematological malignancies, taught by Quesnel B *et al.*, because loss of p53 function is correlated with increased resistance to chemotherapeutic agents, as taught by Lee et al." The Examiner adds that one would have expected that the peptide does not inhibit the DNA specific binding property of p53, and that p53 is activated for DNA specific binding and transcription, "because the peptide taught by Bottger *et al.* disrupts the binding of p53 to mdm2 only at the specific p53 binding site to mdm2, which is expected to be different from the DNA binding site of p53, and because the activity of p53 is to function as a transcriptional factor, via binding to specific DNA, as taught by Lee *et al.* and Bottger *et al.*" From this, the Examiner concludes that one of ordinary skill in the art "would have been motivated to disrupt the biding of p53 and mdm2 in cancer cells that express p53 and mdm2, including those populations of cancer cells that do not overexpress mdm2, with a reasonable expectation of success."

Applicant disagrees, and vigorously traverses the rejection.

The prior use of molecules that inhibit the binding of p53 to mdm2 in cancer treatment was based on the theory that "the overexpression of mdm2 interferes with the normal feedback loop between mdm2 and p53, allowing cells overexpressing mdm2 to escape from p53-regulated growth control by binding p53." (Paragraph bridging pages 1 and 2 of the specification;

emphasis added.) However, as it is explained in the specification, and as the Examiner reiterates citing McCann *et al.*, Quesnel B *et al.*, there are cancers that do not overexpress mdm2. Indeed, as the specification states "overexpression of mdm2 only occurs in a small group of sarcomas." (Page 2,lines 28-29.) As a result, the utility of therapies based on the model of targeting mdm2-overexpressing tumors was rather limited. The key finding underlying the present invention is that mdm2 also binds p53 in cells in which mdm2 is not overexpressed, and that in these cells, this binding interaction targets p53 for degradation (see the passage bridging pages 2 and 3 of the specification). From this unexpected finding, the present inventor concluded that inhibiting the binding of mdm2 to p53 allows levels of p53 to increase by reducing the clearance of p53 by mdm2, and can be used to activate p53 function (page 3, first paragraph). There is nothing in the cited references, when taken alone or in any combination, that would indicate or suggest this finding, which requires the recognition of a different mechanism of action for inhibitors of p53-mdm2 interaction, neither taught nor suggested by the prior art. Thus, prior to the present invention a person of ordinary skill in the art would have had no motivation to try to inhibit the binding of mdm2 and p53 in cancer cells not overexpressing mdm2, since, based on prevailing theory, such inhibition would not have been expected to provide any clinical benefit. Furthermore, even if such motivation had existed, as it did not, one of ordinary skill would certainly not have had any reasonable expectation that such inhibition in cells not overexpressing mdm2 would activate p53 function. Finally, the present rejection is based on the assertion that using the peptide of Bottger *et al.* to disrupt the binding of p53 and mdm2 in tumor cells not overexpressing mdm2 to increase the activity of p53 would result in the invention claimed in the present application. However, this is clearly not the case, since the claimed invention is not based on the use of the peptide of Bottger *et al.*, rather on using peptides comprising SEQ ID NO: 3.

In conclusion, for the reasons discussed above, one of ordinary skill would have had no motivation to try to use the peptides recited in the claims pending to disrupt the binding of p53 and mdm2 in cancer cells that do not overexpress mdm2, and even if such motivation had existed, such person of ordinary skill would have had no expectation that such inhibition would result in any benefit, such as in the increase of p53 activity. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

Finally, it is noted that the statement on page 16 the "[t]his application currently names joint inventors" is incorrect. The sole inventor names in this application is David Philip Lane. If the Patent Office records indicate otherwise, appropriate correction is required.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early issuance of a Notice of Allowance is respectfully solicited.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39749-0001APC**).

Respectfully submitted,

Date: April 18, 2006

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